CBER Office of Therapeutics Research and Review
CBER Office of the Center Associate Director for Research
Product Review: Chemistry, Manufacturing and Controls

BLA 103964/0
PEGASYS™ , peginterferon alfa-2a
(Ro 25-8310 Injectable Solution, 180 ?g/mL)

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Product Review

BLA 103964/0
PEGASYS™ , peginterferon alfa-2a
(Ro 25-8310, Injectable Solution,180 ?g/mL)

CHEMISTRY, MANUFACTURING AND CONTROLS
DRUG SUBSTANCE
VOLUMES/FOLDERS 2.1, 3.1, 4.1 THROUGH 4.15

By

Nga Yen Nguyen

OVERVIEW OF BLA 103964

BLA #	**103964** (**ORIGINAL SUBMISSION**)
Product	PEGASYS™ (PEG-IFN; Peginterferon alfa-2a; peginterferon)
Manufacturer	Hoffmann-La Roche, Inc., Nutley, NJ
Sponsor	Hoffmann-La Roche, Inc., Nutley, NJ
Proposed Use	Treatment of Patient with Chronic Hepatitis C; 180 ?g SC once a week for 48 weeks
Special Request	Priority Review
User Fee ID Number	0136KA1522MAY00
Electronic Submission	None (in the electronic format proposed before June 1, 2000)
Reviewer	Nga Yen Nguyen (FBR/OADR/OD)

Review Responsibility CMC (Drug Substance)

NOMENCLATURE

Proprietary Name	PEGASYS
USA Approved Name (USAN)	Peginterferon alfa-2a
Generic Name	Peginterferon alfa-2a
Code Name	None
Chemical Name	None

PEG-IFN is not currently available in any part of the world. [

]

KEY MANUFACTURING MILESTONES

A number of major changes were introduced after phase III trials. The changes were related to the sources and manufacturing processes of PEG reagent and IFN alfa-2a. They are listed below:

1. PEG REAGENT

- **[**

]

2. PEGINTERFERON ALFA-2a DRUG SUBSTANCE

- **[**

]

[

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3. PEG-IFN ALFA-2a DRUG PRODUCT SOLUTION FOR INJECTION

Vials were initially developed as the drug product and were used in the clinical program. ----------were developed later to address marketing needs. The following dosage forms are included for review:

180 ?g/mL, 1-mL fill in a 2-mL vial

An excess volume is included in both vial and ---------- format to permit withdrawal and administration of the labeled dose.

4. FORMULATIONS

PEGASYS is supplied as an injectable solution in vials and [

]

Vials were formulated with a single dosage of 180 ?g/1 mL of buffer (compared to 0.5 mL for syringes). Recommended storage for both ------- and vial formulations is $2^{o}C$ – $8^{o}C$ ($36^{o}F$ to $46^{o}F$), protected from light. Freezing or shaking of samples should be avoided.

Ingredient	Quantity/mL (Vial)	Quantity/mL ----------
PEG-IFN alfa-2a	180 ? g	[
360 ? g		
Na Acetate Trihydrate	2.617 mg	
Glacial AcOH	0.0462 mg	
0.0462 mg		
NaCl	8.0 mg	
Benzyl Alcohol	10.0 mg	
10.0 mg		
Polysorbate 80	0.05 mg	
0.05 mg		
WFI to	1.0 mL	
1.0 mL		
Final pH	6.0±0.1	
6.0±0.1		]

5. FACILITIES & RESPONSIBILITIES

Hoffmann-La Roche, Nutley, NJ is the license holder for PEGASYS (Government License Number 0136).

- ----------: IFN alfa-2a production and testing.

- ----------

- Hoffmann-La Roche, **Nutley**, **USA**:

  - Vial = production, testing, labeling, packaging and warehousing
  - ----------
  - Quality Control = PEG reagent and IFN release for further processing; final release of peginterferon and drug product (vials and pre-filled syringes)
  - Alternative sites are----------.

- ----------: PEG reagent production and testing.

SUMMARY

Pegylation of proteins by polyethylene glycol has been shown to decrease immunogenicity and antigenicity and to increase circulating serum half-life, stability to proteolytic degradation and solubility in aqueous solutions. Increased solubility in water is the result of hydrogen-bonding of three water molecules per ethylene oxide unit. Singly or in combination, these alterations may increase therapeutic benefits by increasing bioavailability of the active species.

Among approved pegylated products are (i) an intravenous immune globulin preparation “Gammagard” (Baxter healthcare); (ii) ---------- used in the treatment of acute lymphoblastic leukemia); (iii) PEG-adenosine deaminase “Adagen (Enzon, Inc.). Adagen contains almost 400 times the amounts of PEG used in PEG-IFN. It has been shown to be safe and effective in the treatment of severe combined immunodeficiency syndrome SCID, even after four years of

therapy; (iv) pegylated superoxide dismutase; (v) pegylated uricase and, (vi) pegylated interleukin 2.

The material in this BLA is a covalent conjugate of recombinant interferon alfa-2a (20 kDa) with a single branched polyethylene glycol chain of approximate MW of 40 kDa via a stable amide bond. The resulting pegylated interferon alfa-2a has a molecular weight of approximately 60 kDa.

Stability data for the drug substance was generated from material produced at [[

] scale material exhibited satisfactory stability for at least ---- months. Based on analytical comparability (both release testing and extended characterization) between the various PEG reagent and IFN alfa-2a from different sources, the sponsor proposed that the stability profile for the commercial material [

] would be comparable to that of the ------ scale material. Stability studies will continue for a total of --- months. Updated stability data will be submitted, as they become available.

Stability data for the drug product was generated from material manufactured at [

] They demonstrated satisfactory stability for at least 18 months based on PEGASYS vials (--------). The sponsor suggested that marketed PEGASYS vials [

] would display stability profiles comparable to the ----- scale, based on analytical comparability between marketed vials and vials produced at the ----------. Additional stability studies with PEGASYS (180 ?g/mL vial, [

]were initiated in ---------- and would generate --- month stability data by ----------

It is anticipated that the structure of the PEG moiety directly affects the clinical pharmacology of PEGASYS. The size and branching of the 40 kDa PEG moiety define the absorption, distribution and elimination characteristics of PEGASYS. Following a single subcutaneous injection of 180 ?g in healthy volunteers, serum concentrations of PEGASYS are measurable within 3 – 6 hrs. Within 1 – 2 days, 80% of the peak serum concentration is reached and is maintained for 72 – 96 hrs following dosing. The absolute availability of PEGASYS is 84% and is similar to that seen with IFN alfa-2a. There were no reports of acute overdosage in clinical trials with PEGASYS. Weekly doses up to 540 ?g and 630 ?g have been administered in ---------- and ---------- clinical trials, respectively.

The Phase II/III and III pivotal studies consisted of three large randomized, parallel group, statistically powered clinical trials comparing PEGASYS with IFN in 1441 patients with chronic hepatitis C. The Phase II/III study (NV15495) was a trial with 271 patients with chronic hepatitis C complicated by compensated liver cirrhosis or transition to cirrhosis. The two Phases III studies (NV15496 and NV15497) of 1170 patients included approximately 16% of patients with cirrhosis or transition to cirrhosis. Patients were treated for 48 weeks and followed for an additional 24 weeks, with 3 MIU three times per week (NV 15495 and NV15496) or with an induction regimen of 6/3 MIU three times per week.
The primary efficacy endpoints in the Phase III trial are combined sustained virological and biochemical response (loss of detectable serum HCV-RNA/---- and normalization of ALT) at treatment week 24 and at end of follow-up (week 72). Secondary efficacy endpoints include assessment of quality of life, improvement in liver histology at week 72, virological and biochemical response at end of treatment (week 48) and sustained response at the end of treatment, week 72.

The sponsor reported a 30% response rate compared to 6% for Roferon. The sponsor also indicated statistically significant improvement in histological response and HAI scores were seen with PEGASYS, compared to Roferon. The clinical efficacy data submitted in this BLA are derived from a total of 1600 patients randomized to treatment with PEGASYS or Roferon-A for 48 weeks and 24 weeks of follow-up.

Reviewer's comments: At the OTRR presentation and subsequent internal meetings to discuss labeling of the product, it appeared that the report of 30% response rate was not completely accurate, as pointed out by the Clinical Reviewer.

Pre-pivotal meetings were conducted in October 1997. Pre-BLA meetings for Clinical and CMC took place respectively, on March 21 and 23, 2000. The sponsor indicated in this BLA that PK studies would be performed to compare clinical vials [.

]

Reviewer's comments: This statement by the sponsor is incorrect. The sponsor was asked to perform a 3-arm PK/PD study to compare PK/PD data (from vials of phase III material) with vials intended for registration [

] CBER shared concerns with the sponsor that the ---------- formulation with a ---------- ---------- of material may generate additional problems (aggregation, bioavailability, etc.) in PK studies.

The results from the PK studies were received and were reviewed by Dr. David Green in September 2000. The sponsor did not demonstrate

comparability between the commercial material in ---------- and the Phase III material. The sponsor withdrew the ---------- from the BLA in November 2000 and discussed plans for submitting required animal and human PK comparability data with FDA in a November 22, 2000 teleconference.

LIST OF INDs for PEGASYS

[

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ABBREVIATIONS

AAA	Amino acid analysis

AcOH	Acetic acid
AV assay	Antiviral assay
CHC	Chronic hepatitis C
Da	Daltons
DS	Drug substance
DP	Drug product
DW	De-ionized (or distilled) water
^{o}C	Degrees Celsius
^{o}F	Degrees Fahrenheit
GLP	Good laboratory practice
HCL	Hydrochloric acid
HLR	Hoffmann-La Roche
Hr	Hour
IFN	Interferon α-2a, Roferon
IU	International unit
IV	Intravenous
kDa	Kilodaltons
M	Mass or molar, depending on context
Mf1	IFN alfa-2a with the expected structure
mAb	Monoclonal antibody
Met	Methionine

MW	Molecular Weight
N	Number
NA	Not applicable
NaCl	Sodium chloride
NaOAc	Sodium acetate
-----	----------
------	----------
--------	----------
PEG-IFN	Pegylated interferon alfa-2a, Ro 25-9310, PEGASYS
PEO	Polyethylene oxide
QC	Quality Control
-----	----------
----------	----------
SC	Subcutaneous
-------	----------
TCA	Trichoroacetic acid
----------	----------
---------	----------
UV	Ultraviolet
----	----------
WFI	Sterile water for injection
Ro 25-8310	Pegylated interferon alfa-2a
Ro 26-8955	Reactive PEG reagent

INTRODUCTION

Interferon (IFN) alpha belongs to a family of proteins which exhibit antiviral, antiproliferative and immunomodulatory activities. A number of these proteins have been expressed in *Escherichia coli.* To-date, IFN alpha has been approved for the treatment of a variety of diseases, i.e., hairy-cell leukemia, AIDS-related Karposi sarcoma, chronic hepatitis B, chronic hepatitis C (non-A/non-B), condylomata acuminata, to name a few.

The reported elimination half-life for IFN alpha ranges from 4-10 or more hours, with peak serum concentration at 3-8 hrs following IM or SC injection. The frequent administration necessary for sustained efficacy in interferon monotherapy results in several dose-dependent side effects ranging from flu-like symptoms to more pronounced manifestations (fatigue, anorexia, weight loss, transient leukopenia and some psychiatric adverse events such as depression, instability, insomnia, anxiety and suicidal behavior).

The covalent attachment of polyethylene glycol to interferon alfa-2a to produce PEGASYS has resulted in prolonged serum half-life thus reducing administration frequency as well as possible side effects. For example, Adagen (PEG-adenosine deaminase from Enzon, Inc.) has a half-life of 357 hrs compared to 20 hrs for the unpegylated protein.

Interferon afla-2a is a recombinant human leukocyte IFN produced in *E. coli*. The recombinant protein has 165 amino acid residues, ----------, a MW of -------- and a specific activity of 2 x 10^8 IU/mg protein. Pegylated interferon alfa-2a (approximate MW 60 kDa) is a covalent conjugate of recombinant interferon alfa-2a (20 kDa) with a single branched polyethylene glycol chain of approximate MW of 40 kDa via a stable amide bond. Chemically, it is a bis-(N-monomethoxypolyethyleneglycol-urethanyl)lysyl interferon alfa-2a. The branched PEG reagent consists of two 20 kDa monomethoxypolyethyleneglycol chains covalently linked to the amino groups of a lysine via ----------.

[

]

Pegylation of interferon results in less frequent dosing compared to the approved dosage of 3 MIU, TIW administered SC or IV. PEG-IFN alfa-2a conjugate is formulated as a solution for injection in vials and ----------. Based on available stability data, the drug substance and drug product (used in phase III trial) are both projected to be stable at least for -- months at the recommended storage temperature of
-70^{o}C and 2 - 8^{o}C, respectively.

The list of establishments that are involved in the production of PEG reagent, IFN alfa-2a and peginterferon alfa-2a is given on page 5 of this review. Interferon alfa-2a is produced both at the ----------. For the purpose of this BLA, only IFN alfa-2a from --------- will be shipped to Nutley for pegylation and subsequent testing, labeling, packaging in vials and warehousing. ---------- are manufactured in -------- and shipped to Nutley for labeling, packaging and warehousing. All quality control operations are under Nutley's responsibility.
[

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DESCRIPTION & CHARACTERIZATION
(Volume 4.1, pages 1 – 106; Volume 4.2)

A. DESCRIPTION (Vol. 4.1, p. 18 - 20)

Interferon is a 165 amino acid protein with a molecular weight of -------. There are ---------- potential sites (lysine) for pegylation (attachment # # 1). Peginterferon alfa-2a (Ro 25-8310; PEG-IFN) results from the attachment of a ~40 kDa branched polyethylene glycol to lysine residues via an amide bond.

[

]

The reactive PEG reagent (Ro 26-8955) contains two ~20 kDa monomethoxy PEG (mPEG) chains attached to the ? - and ? - amino groups of lysine via ---------- The carboxyl group of lysine is activated to a--------. The activated ----- group subsequently reacts with lysine residues of interferon alfa-2a through an amide bond. The number of repeating ---------- in PEG reagent (average molecular weight 43 kDa) is ----------.

Pegylated IFN alfa-2a has an average molecular weight of ~63 kDa by ----------. The pegylated product consists of a mixture of ~ --- monopegylated IFN and -- of diPEG and oligoPEG IFN. The major pegylation sites have been identified as lysines ----------.

The bulk drug substance is stored in ----------

B. CHARACTERIZATION/PROOF OF STRUCTURE (Vol. 4.1, p. 21-106; Vol. 4.2)

5. Peginterferon Reference Standards (Vol. 4.1, p. 22 – 68)

Two peginterferon Reference Standards were used during development and registration batch release and stability studies.

Reference Standards PEG-IFN DS Manufacturing IFN/PEG reagent Usage

Lot#	lot#	Scale		
----------	----------	---------	----------	DS/DP release, stability
----------	----------	---------	----------	Reg. batch release

The following tests were used to assess the physico-chemical characteristics and biological activity of the Reference Standards.

- Physico-chemical characterization:[

  ]
- Purity: ----------
- Composition and positional isomer distribution: [
  ]
- Protein content: ----------
- Potency: ----------

The MW of mPEG alcohol starting material primarily sets the molecular weight of peginterferon material. The specified MW for PEG reagent is ----------. The MW of ---------- were determined by ---------- to be ---------- and were within specified values for peginterferon alfa-2a MW.

-- analysis of the Reference Standards in the ---------- indicated ---------- that are typical of an alpha helical protein.

The relative % of the ---------- in the two Reference Standards were comparable ---------- for isoforms 1---------- respectively). The four major isoforms represented ~---- of the product.

[

] This value was within established specifications.

[

]PEG IFN represented ----- and ---------- of the product in ----------, respectively (attachment #3). The values were within acceptable limits.

Protein content was determined by---------- ----------the protein content was ---------- and ----------for ----------, respectively. These values were

[

]

Early in development until March 1997, the standard used was ----------
(assigned units = ----- U/mL). It was calibrated against WHO interferon
Reference Standard. Peginterferon Reference Standard ---------- (assigned
unit = ~--- U/mL) was also calibrated against the WHO interferon Reference
Standard. Using this method, initial ----- results for ----------
were ---------- U/mL (---------- U/mg)
respectively. Beginning March 1, 1999, ---------- was qualified for use as a
---------- standard (IND----------)

Stability studies of ---------- was performed for --- months at --------.
Accelerated stability studies were performed at ----. The Reference Standard is
re-tested ----------.

Certificate of Analysis ----------

[

]

[

]

Reviewer's comments: Physico-chemical and biological characterization of the peginterferon Reference Standards was adequate. The data indicated that the standards had the correct primary and secondary structures and were within acceptable limits regarding the relative percent of -------PEG IFN, --PEG IFN and ----PEG IFN. The relative content of the ---- major positional isomers was also within BLA specifications.

5. **Registration Batches** (Vol. 4.1, p. 69-106)

Registration batches represent the peginterferon alfa-2a **commercial drug substance** [

] . They have been characterized by release tests and extended characterization according to BLA specifications.

[

]

PAGE 20 HAS BEEN DETERMINED NOT TO BE RELEASABLE

Page 21 HAS BEEN DETERMINED TO BE NOT RELEASABLE

Registration batches, made with commercial material, were in compliance with BLA specifications with regards to physico-chemical characteristics and biological activity.

5. Interferon Molecule Post Pegylation (Vol. 4.2, p. 1 - 240)

Interferon after pegylation was characterized by the techniques listed in characterization of peginterferon Reference Standards and registration batches (sections 1 and 2 above). The characterization of several lots of pegylated interferon alfa-2a is described below.

Peginterferon	Lot#	IFN	source/scale	Facility
[				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
				Nutley Bldg --
			]	

IFN---------- IFN alfa-2a Reference Standard

---------- Peginterferon Reference Standard
---------- Peginterferon Reference Standard

Characterization Methods and Results

Characterization methods were identical to those used for the characterization of peginterferon Reference Standards and registration batches.

---------- for the first -- amino acids and amino acid analysis indicated excellent agreement with the expected interferon alfa-2a sequence and amino acid composition .
----------indicated that pegylation has not affected interferon primary or secondary structures.
The percent of ----------
----------was determined by

---------- peginterferon lot ---------- and comparing the LC-
---------- data of this ---------- lot with the other lots that were entered in the characterization program . The percent of ---------- product in the lots were estimated to represent ---------- of total product. The BLA specifications allow up to ---------- product.

Reviewer's comments: As indicated in earlier comments, -------- is a qualitative method and the relative ---------- percent observed on the ---------- does not necessarily represent the actual ----------. Further, the low level of ---------- in peginterferon samples could be accounted for by ---------- that may already be present in the starting IFN alfa-2a material.

- [

]

Reviewer's comments: Pegylation at a lysine residue would have the following results; [

]

Reviewer's comments: The overlapping of ---------- indicated that molecular secondary structure has not been affected by pegylation.

- [

]

Reviewer's comments: Until March 1999, peginterferon Reference Standard lot ----------, with assigned units of ------ U/mL was used. This batch was calibrated against the WHO interferon Reference Standard. In March 1999, the Reference Standard was changed to ---------- This standard was NOT calibrated against the WHO interferon Reference Standard, but was given an assigned unitage based on its EC_{50} (----------). The amendment requesting change in reporting of unitage (IND ----------) was reviewed and approved in August 1999.

[

]

- [

]

Reviewer's comments: The methods were tested for system suitability and acceptance criteria. They were validated with regard to specificity, linearity, accuracy, precision, reproducibility (same day runs and runs performed on different days) and ruggedness (inter-analyst precision, instrument-to-instrument, column-to column, lot-to-lot variability, source of ---------- etc.).

4. **Biological Activity** (Vol. 4.3, p. 205-210)

The biological antiviral and antiproliferative activities of IFN are reduced by pegylation. This decrease in biological activity is counterbalanced by an increase in *in vivo* half-life that provides sustained therapeutic concentrations and greater efficacy than unmodified interferon. Biological activity is expressed as "bioassay units" (ICH and USP guidelines).

5. **Peginterferon Reference Standard Calibration History**

Peginterferon Reference Standard was calibrated against the WHO interferon Reference Standard and was assigned a unit value of --- U/mL for a ---------- stock solution. During the course of development, the sponsor revised the definition of biological activity unit as the ---------- ----------. This revision was reviewed and approved by FDA in August

1999 (IND ----------). To determine the new unit value, peginterferon reference material was analyzed in one or more assays on each of --- different days. Extreme values were ignored and the arithmetic mean of the dilutions at ------- inhibition was calculated for each assay and each day. The logs of the arithmetic means were averaged and the antilog taken to determine the geometric mean over ---- days. This geometric mean is the assigned unit value of the Reference Standard for a -------ng/mL stock. This value was ---------- (rounded to ----- U/mL) and was put into effect on March 1, 1999 For comparison, biological activity values generated before March 1, 1999 must be divided by --in order to be compared to data generated after this date (**Old Standard = -- IU/ng. New Standard = -- U/ng**). A comparison is listed below with -- analyses of -- lots of 180 ?g/mL drug product ---------- ---------- The old standard was ---------- and was calibrated against WHO IFN standard. The biological unit for the new standard ---------- was based on ------.

From the review of the data, the range of biological activity ---------- (with the old standard) is comparable to that calculated with the new standard, ----------

.

Specific Activity (U/mg)	Old Standard (------ U/mg)	New Standard (----- U/mg)
Range	[	
Average		
Standard deviation		
% RSD		
N		]

Qualification of a New Reference Standard

A new peginterferon Reference Standard will be prepared from commercial material----------. The new Reference Standard will be used as an in-house standard for biological activity and will be calibrated against the WHO IFN Reference Standard, as opposed to ------, as is currently the case. The new Reference Standard will be tested against the WHO on a regular basis over a defined period of time to generate a representative data set. Lot ----------is now tested against the WHO IFN Reference Standard in order to generate historical data to support the calibration of the new peginterferon Reference Standard.

Reviewer's comments: The rationale for switching back to qualification of a new Reference Standard by calibration against the WHO IFN standard (as opposed to the currently used and approved ------- method was not clearly described. This question was communicated to Debra Savuto (outgoing teleconference on December 05, 2000 followed by incoming teleconference

on December 07, 2000). In this teleconference, the sponsor indicated that calibrating against the WHO IFN Reference Standard was needed in preparation for global harmonization.

A written response to this question was received on January 4, 2000.

6. Antiviral Activity: Proposed BLA Specifications

[

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---------- ---------- ---------

Unmodified IFN alfa-2a

A validation study was conducted to determine the maximum amount of unmodified IFN that could be present in a bioassay sample without significantly affecting biological assay results. The [

]

MANUFACTURE

(Vol. 4.4, p. 1 – 26)

This section identifies the facilities where production (Biopharmaceuticals Dept. ----------, Nutley NJ) and testing (Quality Control laboratories --------- and ------, Nutley NJ) were performed. A description is also given regarding floor diagrams, contamination precautions, manufacturing air classifications, equipment design, other products, cell bank preparation controls and in process control for contamination prevention. This section is under the review responsibility of CBER ELA/QC groups.

METHODS OF MANUFACTURE

(Vol. 4.4, p. 27 –317; Vol. 4.5 p. 1 – 128; Vol. 4.6 1 – 202 and Vol. 4.7 all)

A. RAW MATERIALS AND REAGENTS (Vol. 4.4, p. 27)

1. Pegylation Process Raw Materials (Vol. 4.4, p. 27 –147)

[

]

2. PEG Reagent Ro 25-8955

PEG reagent is a ----------of bis-(methoxy-polyethylene glycol, MW 20000)-modified lysine (attachment #10). ---------- batches of PEG reagent, ---- from ----------were tested. Supplier's test results may be accepted by HLR for all tests except appearance, color and identity tests.

- **HLR Certificate of Analysis for Release**

[

]

[

]

- **Validation of Identity Test: ----------**

The method was validated with regards to:

- Specificity:[

  ].
- Precision: ----------.
- Resolution: [

  ].
- Robustness: [

  ]

B. PEG REAGENT Ro 25-8955 (Vol. 4.4, p. 148 – 317)

1. Description

- The MW of the PEG reagent is a range of MW based on the number of repeating ----------that make up each arm of the branched PEG molecule. This heterogeneity is typical of all polymers including ----------, which is a starting material for PEG reagent manufacturing. The MW of PEG reagent is controlled through a uniform raw material release specification and testing program at ---------- facilities. The ---------- starting material has a MW specification of----------. The PEG reagent release specification for MW is ----------.

- ---------- measurement of the PEG reagent ensures that its molecular weight is controlled within an acceptable range.

2. PEG Reagent Reference Standard

A new Reference Standard from the final commercial process, ----------was certified as the in-house Reference Standard for both ---------- after characterization by release testing and extended characterization methods. This standard has been qualified and documented using the --- qualification procedure. It has been distributed to -----.

Certified ---------- MW standards were used as MW standard for PEG reagent. The ----- standards have a distribution of MW that bracket the PEG reagent MW

3. PEG Reagent Comparability

- **Overview**

PEG reagent was developed and produced by----------. The earliest batches were used in the development and clinical supply of peginterferon alfa-2a and were produced at ----- facility in ----------. Synthesis started with production of a ---------- activated ---------- that subsequently reacted with lysine to form [

]

The most critical feature of PEG reagent is its --- that is primarily set by the ----------. The PEG reagent --- specification of ---------- have remained constant from the earliest batches through current batches produced at both ---------- facilities. Characterization data for the -- lots of ---- that were used to produced **clinical lots** of drug substance is shown below.

[

]

Reviewer's comments: Results from the characterization of -------- batches of PEG reagent indicated values that were within BLA specifications. A specification of ------- ----------for was added after the early PEG reagent lots were made.

- **PEG Reagent Comparability Strategy and Plan**

- Common method of manufacture at both ---------- facilities
- Establishment of common specifications
- Comparability Plan: (i) comparing testing results from ---------- consecutive batches with established specifications, (ii) extended testing of the ---------- batches by ---------- and, (iii) testing against a Reference Standard (reflective of PEG reagent used in clinical lots) as both IFN and ---------- derivatives by ----------
- The ----- consecutive batches that were entered in the comparability studies were ----------. They were produced by ---------- process. ---additional ---------- PEG reagent, ---------- ---------- will also be tested.
- Further verification at the drug substance level

In order to demonstrate comparability between ---------- PEG reagents, the ------- consecutive batches must meet or exceed release specifications listed in sections 4 and 5, below.

- **PEG Reagent Reference Standards**

Batches of -------Reference Standards used in comparability studies were ----------

4. Evolvement of Specification Setting

During the course of development, specification setting has evolved and has been tightened. Specifications for [

]. Revisions to specifications for clinical and current commercial PEG reagent are listed below.

Specification	PEG Reagent (Clinical Lots)	PEG Reagent (Commercial Lots)
[		
		]

[

]

C. PEG REAGENT FROM ----------

Preclinical and clinical supplies of peginterferon were prepared with PEG reagent from ----------. The final commercial product was produced at ---------- A key manufacturing change was the addition of [

]

Other names for PEG reagent are ----------. The PEG reagent is classified as a --------- Drug master File (----------).

- **PEG Reagent Process Development Summary**

- [

]

PAGE 35 WAS DETERMINED TO BE NOT RELEASABLE

PAGE 36 WAS DETERMINED TO BE NOT RELEASABLE

PAGE 37 WAS DETERMINED TO BE NOT RELEASABLE

[

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Reviewer's comments: Values from the certificates of analysis of the ---------- batches were comparable and were within acceptance specifications. The results supported analytical comparability of PEG reagent made at the ---------- facilities using ---------- manufacturing process.

1. Release Criteria: Phase III and Commercial Material

Assay	Phase III	Commercial
[		

]

[

]

Reviewer's comments: (i) % purity = 100% - total impurity%; (ii) % PEG3 is determined during in-process testing of the PEG acid; (iii) Total impurities = PEG1 + PEG1' + PEG3 + PEG 4 + PEG acid + other.

2. Stability Program

Stability studies were initiated for ---------- products and were intended for a total duration of --- months. The main degradation product , ---------- ---- would reduce the amount of active PEG reagent available for protein modification. Initial data for -- batches of -------- stored at ---------- indicated adequate stability for ---- months for 1--batch and -- months for the other ---------- material will be re-tested ------. The ---------- stability program was initiated in December 1999 and will continue through 2002.

D. PEG REAGENT FROM ----------

1. Overview

----------. transferred PEG manufacturing technology to a secondary manufacturing site located in ----------. Additional testing/extended characterization of --- material may be performed by ----.

2. Manufacturing Steps (attachments # 12a-b)

[

]

✓

PAGE 40 WAS DETERMINED TO BE NOT RELEASABLE

[

]

Acceptance criteria data for the three validation batches are summarized below:

[

]

Reviewer's comments: The sponsor provided a discussion of process deviations and temporary process changes for the two batches which were reprocessed.

3. Process Validation Report

The chemistry, equipment and procedures were essentially the same as those used at ----, through technology transfer. A total of --- batches were produced. ------- consecutive ------- batches ---------- were used as validation batches and were intended for commercial use. Comparison of analytical data with release specifications showed conformance to release specifications.

E. PEGYLATED INTERFERON ALFA-2a

1. Interferon alfa-2a

Interferon alfa-2a was produced in [

]. It was stored and shipped at --------

---------- The bulk IFN was released, based on ---------- certificate of analysis and positive identity test from ----------. A minimum of ---- and maximum of ----- were ----------). The ----- IFN material could be stored up to ----------.

2. Pegylated Interferon alfa-2a

[

]

Reviewer's comments: All raw materials used in downstream processing were segregated from Quality Management released materials. Quarantined materials were adequately labeled, waiting to be either released or discarded upon re-testing. [

].

3. Use and Reuse of ----------

[

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F. PURIFICATION PROCESS DEVELOPMENT

[

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PAGE 44 WAS DETERMINED TO BE NOT RELEASABLE

PAGE 45 WAS DETERMINED TO BE NOT RELEASABLE

Certificates of analysis for ---------- were provided for review. The lots were produced with ---------- and were analyzed and released by the----------.

[

]

G. COMPARABILITY ASSESSMENT OF PEGINTERFERON ALFA-2a

4. Background and Summary

Data was provided in support of comparability of the (i) commercial peginterferon alfa 2a with the clinical material and (ii) pegylating reagent from [
]

Peginterferon was manufactured at scales of ---------- at Nutley, New Jersey.

IFN-α	PEG reagent	DS for Study Phase	Production Scale
----------		Clinical	---------
----------		Commercial	---------

Reviewer's comments: The commercial process peginterferon alfa-2a consists of peginterferon alfa-2a manufactured at the --------- at Nutley, using IFN alfa-2a from ------- increased ---------- process and PEG ---------- facilities.

4. Comparability Approach

Programs to establish comparability between the peginterferon alfa-2a commercial and clinical materials were reviewed in the "Methods of Manufacture" section above. In this section, only comparability of the drug substance will be reviewed with regards to: (i) bridging the ---------- processes to the ------- scale production process, (ii) release testing and extended characterization for the ---------- lots (from the low ---------- process), (iii) full release and extended characterization for co-mixture studies (---------- registration lots) and, (iv) stability data (----------). The list of lots and lot classification is given in attachment # 13.

- Production: During the course of production, the batch size of peginterferon production was scaled up from ---------- , then from ----------of the IFN starting material.
- [

]

- Release testing results: Certificates of analysis of the ------ registration lots,the ---------- validation lots (from ---------- IFN), ----------validation lots and -- clinical lots were submitted for review. To establish comparability, results for the -- registration batches were evaluated against both the specifications established for comparability and with BLA specifications. A comparison of the IND specifications at the time of pre-BLA meeting, comparability specifications and proposed BLA specifications is given below. BLA specifications were derived from the comparability specifications which included clinical experience and analytical limits of the methods. Results were also evaluated against the trends and ranges for bulk clinical lots.

[

]

[

]

Reviewer's comments: Review of the data provided in attachments # 14 – 18 in support of product comparability indicated that peginterferon from the---------- were comparable with regards to purity (% ----------PEG reagent impurity removal ----------

4. Co-Mixture Studies

[

]

[

]

Reviewer's comments: All values are within BLA specifications.

[

]

Reviewer's comments: Review of release testing results (physico-chemical, biochemical, *in vitro* biological activity) and co-mixture studies indicated adequate comparability between registration and clinical lots. Comparability of the additional ----------lots was also demonstrated by release testing results.

4. Extended Characterization

Extended characterization was used to confirm peginterferon identity from all manufacturing scales and to support comparability between the commercial and clinical material. Extended characterization methods include----------,

[

]

Reviewer's comments: Except for co-mixture lot ---------- claim), all other lots were within the specified ----------label claim. This mixture was prepared with clinical lot ------- which had been stored for -- years at ----. The sponsor believed that because of the storage conditions, the results might not reflect the results that would be observed with storage under BLA conditions (-70^{o}C).

4. Stability

To further assess comparability, stability of peginterferon was assessed at the recommended storage temperature (-70^{o}C) and under accelerated conditions ----------. Testing was performed at ---------- intervals for the ---------- and ---------- interval thereafter. Stability tests included [

]

[

]

Stability studies were provided for registration lot ---------- (attachment #18), supportive ------ lots (attachment # 19) and ----- lots (attachment # 20). Attachment # 21 gave a summary table of stability data. [ ] are described in attachment # 22 (----------) and attachment # 23 (----------). The sponsor also provided ---------- data as additional support for comparability between the clinical and commercial lots.

Reviewer's comments: Accelerated testing was discontinued after -- months at -------- In general, all lots met BLA specifications when stored at ---------- for the specified testing duration. At this time, available stability data on the commercial material (between ----------) remains too limited to allow for an accurate determination of shelf-life.

PROCESS CONTROLS

(Vol. 4.8, p.1 –125)

The IFN and PEG reagent sources are described in attachment # 24. Acceptance criteria included the following requirements: (i) the product was made according to SOP and production batch records. All completed production batch records must be reviewed and approved by the quality unit; (ii) the drug substance must meet the quality unit release specifications for the certificate of analysis and (iii) the in-process control samples must meet the acceptance criteria outline in the validation protocol. Representative test methods,

acceptance criteria, and results for in-process controls are given below and in the corresponding attachments.

[

]

REFERENCE STANDARDS

(Vol. 4.8, p.126-130)

PRIMARY REFERENCE STANDARD

--- pegylated interferon Reference Standards have been used during development and for batch release and stability studies. They were stored in -- -- ----------. Testing showed that the Reference Standards met both the IND specifications under which they were released and the proposed BLA specifications (attachment # 33).

For biological standard calibration, Reference Standard lot ---------- was calibrated against the WHO IFN standard and the unit value was set accordingly. Reference Standard ---------- was calibrated independently of the WHO IFN standard and the unit value was based on the ----------. The assignment of unit value based on -------- will not be applied to new Reference Standards. New Reference Standards will be calibrated against the WHO IFN standard. Reference Standard ---------- is being tested against the WHO IFN standard in order to gather data to support the calibration of a new Reference Standard against the WHO standard.

A new Reference Standard will be prepared using material from the final commercial process. It will be characterized by----------.

Lot	Time	Type	DS Lot	IFN
[				

]

Stability Testing

Stability testing indicated that the Reference Standards were stable at the recommended storage temperature of ---------- in ---------- containers (attachments # 34a-b and 35a-b) according to IND specifications at the time of Reference Standard manufacture and proposed BLA specifications.

SPECIFICATIONS/ANALYTICAL METHODS

(Vol. 4.8, p.137-230; Vol. 4.9)

A. SPECIFICATIONS

The proposed drug substance specifications and analytical methods have been developed in parallel with the clinical and technical development programs to ensure the identity, purity and potency of pegylated IFN alfa-2a.

[

]

Proposed BLA specifications are listed below.

[

]

[

]

B. ANALYTICAL METHODS

This section describes the justification for each proposed specification as well as a summary of development, rationale and supportive data.

[

]

.[

]

2. Lot-to-lot consistency: Evaluation of lot-to-lot consistency was performed by [

]

[

]

Reviewer's comments: The immunogenicity characteristics of the oxidized peginterferon species present in the drug substance may present a safety issue. No immunogenicity data was submitted for review in the drug substance section. Immunogenicity data should be described in the drug product section. The sponsor indicated that only in stressed samples could a distinct and possibly large enough shoulder be detected, resolved and quantitated.

Other minor impurities consisted of the ---------- and other unknown impurities which were only detected in stressed samples. The ---------- impurity was controlled by specifications of ----------. The unknown impurities in stressed samples were small in number and concentration, and ---------- ---- ----------

Both peginterferon and unmodified IFN are biologically active in ----------. ---------- present in the drug substance at levels ---------- interferes with biological activity determination. The release specification of ---------- provided assurance that the bioassay would not be adversely affected by the presence of ----------.

Reviewer's comments: With the exception of lot---------- ----------, free IFN has not been detected either in initial release or stability (under recommended storage conditions).

Residual Free PEG: Release specifications were set at ----------. The removal of free PEG vas followed throughout development and in-process testing. This method was included as a ---------- in May 1998, starting with lot ----------

2.---------- [

]

3.---------- :[

]

[

]

5. Testing program changes: With the proposed BLA specifications, changes were introduced to the testing program.

[

]

- [

]

Reviewer's comments: The proposed specifications and analytical methods have been developed in parallel with clinical and technical development programs. Except for the revision in reporting ---------- ---------- the reviewer feels that the revisions would not significantly affect evaluation of the drug substance identity, purity, ---------- The list of drug substance lots that were used to establish specifications is given in attachments #37a).

METHOD VALIDATION

(Vol. 4.9, p. 1 – 333; Vol. 4.10, p. 1 – 111)

Test methods were analyzed with regards to specificity, accuracy, precision, linearity, range and robustness using peginterferon Reference Standard as well as drug substance and drug product samples. Depending on the test, samples were analyzed in ----- replicate assays by different technicians and on different days (precision, repeatability and ruggedness), -- concentrations in duplicate (linearity) and accuracy (spiked diluents). Robustness of the methods was evaluated by various factors depending on the method [

] Validation of methods is discussed in other sections of this review when applicable. Below is a table that summarizes validation values for peginterferon drug substance.

Test	Specificity	Accuracy	Precision	Linearity*	Range*	LOD/LOQ %

[

]

Reviewer's comments: The list of lots and their classification are given in attachment #13. Of the validation batches, only batches [

] were clearly described with regards to the lineage of pegylating reagent and interferon alfa 2a. The lineage of peglating reagent and interferon components for ----- lots ---------- ---------- were not given. This should not represent a problem since there was not production and or characterization issues associated with ------ interferon.

CONTAINER/CLOSURE SYSTEM

(Vol. 4.10, p. 125-154)

The purified pegylated interferon is aseptically filtered and stored frozen at –70^{o}C± 10^{o}C in sterilized ---------- bottles. This section provides an evaluation of extractables and a validation of autoclave sterilization of the bottles prior to use.

Extractable Evaluation: the drug substance was stored in ---------- bottles ---------- Extractable profiles were determined by [

]

[

]

<u>Reviewer's</u> <u>comments</u>: Given that the extracting power of ---- is approximately 37-fold lower than that of --------- and considering the fact that the bulk PEG-IFN was stored in ---------- buffer, the data presented for review appeared reasonable. The potential for contaminants leaching into the final dosage forms did not appear significant.

PEGINTERFERON ALFA-2a STABILITY

(Vol. 4.10, p. 154-224)

A. OVERVIEW OF PEGINTERFERON alfa-2a DRUG SUBSTANCE STABILITY

The stability of peginterferon drug substance was tested as part of an ongoing ----month program that included peginterferon from the final commercial process ----------. It was designed to evaluate the stability of the registration batches and clinical material.

Supportive stability includes material produced at the[

]

Report #	Type/# of Lot	IFN Source	PEG Source	Stability Storage Conditions
N-181456	Commercial	----------	----------	------- month ----------
N-181640	----------	----------	----------	------ and accel.
N-181455	----------	----------	----------	---------- --- and accel.

-- additional commercial lots have been added to this stability study.

Updates for the commercial material will be provided after the first ------ month time points. Updated stability for the 25 g scale will be provided after the first --- month time point.

Reviewer's comments: Stability data provided with this BLA indicated that the ---------- material demonstrated adequate stability for 18 months. The sponsor stated that this stability profile was an appropriate predictor of shelf life based on the demonstration of analytical comparability between the clinical and commercial material. Since there was only --- month stability data for ---- commercial -----, the reviewer did not find that stability data of the commercial material was sufficient to allow for an accurate assessment of stability.

Updated stability data was provided on August 31, 2000 for a total of -- months stability on ------ and -- months stability data on ---------- of commercial material. A review of updated stability data is given at the end of this document.

B. STABILITY PROGRAM FOR MARKETED PEGINTERFERON alfa-2a

The sponsor indicated that a minimum of --------- lots under different storage conditions in ---------- screw top containers will be placed in the stability program. Thereafter, a minimum of ---------- per year will be placed in the program. If there are revisions which might significantly affect stability, then -- lots of drug substance will be placed into the program. Test methods include:

[

]

Test Stability Specifications Test Result (-70°C)
[

]

Reviewer's comment: The ---------- stability data indicated that the drug substance was stable for ----------at –70°C. It should be suitable for formulation when stored under the –70°C recommended temperature. Updated stability data was provided for review on August 31, 2000. Please see review of updated stability at the end of this document.

C. SUPPORTIVE DATA

Supportive data from the ---------- stored at the recommended temperature of –70^{o}C (----------) are presented below.

1.

- Lots:----------. Stability data for the ---------- lots are given below at the selected time points of ---------- months among the -- time points of ----------months.

Test	Test Result (-70^{o}C)
[	

]

Reviewer's comments: Results were compared to a bioassay reference material that was calibrated against the IFN WHO standard for time points before -- months. The reference material used for time points after -- months used a unit value based on----------.

PURIFIED INTERFERON ALFA 2a
(Vol. 4.11, p. 1-229)

A. DESCRIPTION AND CHARACTERIZATION

Established USAN name: Interferon alfa-2a, recombinant/Roche.

Interferon alfa-2a is a protein solution in a 25 mM ammonium acetate buffer of pH 5.0 containing 120 mM NaCl. The protein concentration is a 1-2 mg/mL. Interferon alfa-2a is a ---------- monomeric, 165 residue protein containing ---------- (Attachment # 38).

1. Characterization/Proof of Structure (Vol. 4.11, p. 3 – 202)

1.1. **Background**: IFN alfa-2a is the product of a cloned human leukocyte interferon gene expressed in *E. coli*. All clinical batches of pegylated interferon were manufactured using the same IFN as for the approved Roferon. The Roferon IFN is produced in [

]

1.2. **Comparability Approach** (Vol.. 4.11, p 7-12)

- [
-
-
-
-
-
-
-

-]

[

]

Parameter	IFN	# of Consecutive Batches
Process Performance		
[		
		]
Release testing	[	
		]
Characterization	[	]
	---	---
Stability		
Accelerated	---	

Real time	---	

1.3. **Comparability assays:** The list of assays used for comparison of purified IFN alfa-2a from the ---------- processes is given below:

[

]

1.4. **Production performance** (Vol. 4.11, p. 12-20)

[

]

Reviewer's comments: One of the ---------- batch from the ----------) was ---------- step. Only data up to the ---------- step were included to increase the size of the comparability database. Data from this ---------- batch were not included in statistical analysis. The sponsor describes in this BLA a procedure to follow for ---------- Please refer to the section on ---------- in this review.

[

]

[

]

Reviewer's comments: values for all ---------- batches were within established and approved in-process controls for the -------- process. The analytical results ---------- indicated a
[

]

[

]]

Reviewer's comments: Although the step yields were comparable between the ---------- processes, the overall yields (g/kg) were lower for the ---------- material compared to the current process, considering a ------ scale-up in production. Since refolding of the ---------- material was [

]

Reviewer's comments: The removal factor for process related impurities indicated that the ---------- process was comparable to the ---------- process [

]

During the course of the review, the sponsor notified CBER that the ---------- facility was experiencing problems with unacceptable levels of *E. coli* protein and would not be ready for the pre-approval inspection planned for ----------

1.5. **Analytical Characterization** (Vol. 4.11, p. 20)

- **Release test methods and specifications** for IFN alfa-2a were transferred [

]

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1.6. **Stability**

- **Accelerated stability**: material from batch ---------- were stored in ---------- vial (packaging material for purified IFN) and stored at ----------. They were tested at ---------- points with regards to ---------- All batches were within ---------- specifications when stored for ----------. However at this temperature, ----------.
- **Real time stability**: ---------- batches of IFN from each process were stored at the recommended temperature of –70°C. **Only ---------- month of stability data was available for review at the time of receipt of this BLA.**

Reviewer's comments: The sponsor's approach for demonstrating comparability between IFN produced by the current (-------) and ---------- ----------) was to (i) assess process performance by comparing in-process data ---------- (-------), (ii) compare release data to ----------) in comparison to ------- material and, (iv) evaluate product stability profiles in comparison with ---------- IFN. The data provided support to demonstrate product comparability except ----------. However, *E. coli* proteins were still within the specified ---- ng/mg purified IFN.

2. Characterization and Proof of Structure

[

]

- Reviewer's comments: In ---------- analysis of peptides and proteins, recoveries of residues such as ----------, [

[

]

Reviewer's comments: Vol.. 4.11-46, ---------- analysis, Material and Methods. The reviewer believes that there is an ---------- ----------. The sponsor is asked to comment on this question.

[

]

[

]

<u>Reviewer's</u> <u>comments</u>: Qualitatively, the ---------- of IFN alfa-2a from the various ---------- did not exhibit significant differences with regards to the presence of ----------products. Quantitatively, the levels of ----------

- Structure and biological activity of IFN alfa-2a variants

[

]

[

]

3. Physico-chemical Characterization

-------batches each of low ----------) were compared to the Reference Working Standard ----------

[

]

Reviewer's comments: The ---------- represented all other IFN-related species, including ----------. Although the ---------- is ----------

[

]

[
].

4. Biological Activity

All ------- IFN batches under testing and the IFN variants exhibited biological activity comparable to the expected specific activity of ----------.

Test sample Specific activity ----------
[

]

B. MANUFACTURER

1. Responsibilities

- Roche Nutley (license holder, # 136)

- Manufacturing, control and product quality issues associated with PEGASYS
- PEGASYS vial finished product production
- ----------
- Complying with FDA cGMP and SOP in the manufacture, testing and release of vial finished product
- Generating, reviewing and approving documentation associated with vial finished product 9----------
- Conducting compliance audits for vial finished product manufacturing and ----------
- Testing and disposition of vial finished product, including stability testing
- Perform identity testing on ---------- IFN prior to final release.
- Perform identity testing on ------- ---------- prior to release
- Responsible for final release of ---------- to USA market
- Responsible for vial ---------- shipping requirement to customers, distribution centers and product recall in USA
- Responsible for all contact and communication with FDA and for all regulatory submissions to FDA
- Responsible for conducting clinical trials using PEGASYS
- Responsible for labeling and advertising materials for USA

- Responsible for reporting adverse reactions in USA
- Reviewing and inspecting all product quality issues
- All changes are reviewed by the Global Change Commission. Where changes impact the US license, Nutley will receive appropriate change documentation for regulatory evaluation
- Participating in compliance audits (with the Pharma Division's Quality Surveillance group) pertaining to the manufacture of PEG reagent, IFN, DS, vial ---------- products

- ---------- is responsible for all operations related to ----------. That includes: (i) manufacture, testing, stability and facility-related issues, (ii) compliance with all cGMP, FDA requirements, SOPs , (iii) review of documentation related to manufacture and control, (iv) compliance audits, (v) export packing and shipping requirements to Roche Nutley, (vi) identify and onsite representative to communicate quality issues and annual report to the Authorized contact.

- ---------- is responsible for the overall manufacture and control of IFN alfa-2a. That includes:

- Raw material control, IFN production, testing and release, in-process testing, facility, systems, process validation and stability testing
- Compliance with cGMPs, FDA requirements and SOPs in the manufacture, testing and release of IFN
- Generating, reviewing and approving documentation associated with IFN production
- Conducting compliance audits (including self-audits) pertaining to IFN production
- Responsible for IFN testing and disposition before shipping to Roche-Nutley
- Responsible for all export packing and shipping requirements to maintain product integrity ---------- during shipping) and shipping to Roche-Nutley in a timely manner.
- Identify an on-site representative to communicate/provide product quality issues and annual reporting documentation to the Authorized Contact in periodic schedule
- The ---------- ------- is responsible for communicating to the Authorized Contact (Nutley) change control documentation related to processing, specifications and methods for IFN

<u>Reviewer's</u> <u>comments</u>: Hold times and shipping conditions were not clearly described for peginterferon material and for the pegylating reagent.

2. Production Facility

At the ---------- site, different biologic and biotechnology derived products for therapeutic use and for biochemical and diagnostic applications, are produced in

different buildings by different campaigns. The biotechnology derived products and active pharmaceutical ingredients (APIs) are manufactured in ----------
[.

]

3. **Water System**: potable water, purified water type I from which purified water type II (PW II) derives. The quality of purified water II is equivalent to WFI according to USP.

Parameter	Value
Conductivity 25°C	≤1.3?S/cm
TOC	≤0.5 ppm
Endotoxins	≤0.25 EU/mL
Bioburden	≤0.1 CFU/mL
E. coli, coliform microbes, Faecal streptococci	negative
Heavy metals	corresponds

PW II is used for all process steps in IFN alfa-2a production (preparation of
[

]

Reviewer's comments: The sponsor did not specify the "accessible" points of use or the number of PWII sampling points prior to final delivery to the equipment or prior to its use in preparing buffer solutions and fermentation media.

4. Other Products

The new Biologics facility for production of bacteria-derived recombinant proteins was designed as a multi-purpose facility to be used on a campaign basis, i.e., only one product will be manufactured at a time within one area. At the current time, only IFN alfa-2a is produced in the facility. The following procedure will be used upon introduction of new products. For example, (i) only licensed or qualified clinical products will be made in the new Biologics facility, and (ii)

measurements have been developed to prevent cross-contamination and ensure product integrity and quality:

- Campaign mode of operation
- Changeover procedure
- All documentation, materials, cells and bulk substance associated with the previous product must be removed prior to a new campaign
- Processing equipment has been cleaned and inspected, rooms and work surfaces have been cleaned per appropriate SOP
- Validated cleaning procedures have been developed for sanitization of premises, outer surfaces, process equipment inner surfaces
- Dedicated equipment: ---------- dedicated to IFN alfa-2a
- Single use equipment: ---------- (storage of biomass) and ---------- bottles (storage of purified IFN alfa-2a)

5. Contamination Prevention

Contamination is controlled through product segregation, performing process steps in closed systems, regular cleaning and sanitization of facility and equipment, compliance to personal hygiene SOP, development of monitoring programs for room classification ----------
---------- and routine environmental assessment.

[

]

[

]

<u>Reviewer's</u> <u>comments</u>: The sponsor did not provide a procedure for ensuring accuracy and reliability in delivering the correct chemicals and volumes during this ---------- step. For example: (i) How many

people are in the laminar hood room at a time? (ii) Is there additional personnel to check the principal operator? (iii) how was aseptic operation ensured, in addition to a ----------

[

]

1. **Flow Charts** (Vol. 4.12, p 154-171; also attachments # 49 – 52)

[

]

[

]

Reviewer's comments: There is no information in this section on (i) available numbers and storage locations for ----------.

[

]

2. Flow Systems (Vol. 4.12, p. 159-171)

2.1. Flow of equipment:

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Reviewer's comments: There is no information in this section on (i) available numbers and storage locations for WCB and MCB, (ii) segregation of *E.coli* from mammalian cells, (iii) presence of locks on liquid nitrogen tank, (iv) monitoring of liquid tank temperature and, (v) accessibility rules.

2.2. Production of new WCB and requalification of MCB and WCB: The majority of the MCB and WCB vials are stored in ----------. A total of --- MCB and --- WCB vials were transferred from -------- and Nutley to ---------- for routine production of purified IFN alfa-2a.

The MCB is stored ----------for complete revalidation. ---------- is re-tested every -- years for viable cell counts ------- cfu/mL) and ---------- resistance --------- according to ICH Q5D Guidance "Quality of Biotechnology products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products". Upon production and release of a new WCB from the MCB, this time point will start a new point for the ---year re-testing cycle. If a new WCB was needed, -------- vial of ---------- will be used to prepare at least ---------- vials of WCB. The new WCB will be re-tested as follows:

[

]

Stability of the WCB was monitored by evaluating the consistency of the IFN fermentation process. Each fermentation process started a new -- years retest interval.

Reviewer's comment: The sponsor did not describe what would be done if interferon alfa 2a production was interrupted for more than --- years.

[

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Reviewer's comments: A few tests, which have been part of the ------- routine testing program, were not performed on a routine basis at ---------- ----------. They were performed only on every ---------- batch and on the ---------- batches produced after a change: ---------- ratio. The rationale was that removal studies showed consistent removal capability of the purification process with regards to ----------. The verification ---------- and determination of ---------- ---------- are now covered by ---------- ----------

The current specifications for ---------- IFN alfa-2a introduced the following revisions in Version 3.0: removal of N-terminal sequencing, DNA testing, copper determination, norleucine/methionine ratio and amino acid analysis.

In view of recent problems with unacceptable amounts of ----------, the reviewer recommends that BLA procedures be strictly adhered to. Deviations from BLA established procedures should be thoroughly investigated and documented.

C. METHOD VALIDATION (Vol.4.15, p. 1-107)

In order to establish comparability and to evaluate the quality and stability of ---------- IFN, a set of analytical methods was transferred from ---------- Quality Control to ---------- Quality Control for evaluation of content, purity, potency and identity. Equivalence and validation were evaluated by comparison of analytical data from three representative ------- ---------- and the current reference standard ----------

Method	Testing for	Type / other	Release Tests

Test methods were analyzed with regards to specificity, accuracy, precision, linearity, range and robustness. For repeatability, ---- replicate analyses were performed; For intermediate precision, analysis was performed by ------ different technicians, on different days, with different sets of solutions and batches of chromatography column. For robustness, analysis was performed with different parameter settings.

Test	Specificity	Accuracy	Precision	Linearity	Range	Robustness

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2 ● Overview of Nutley Release of IFN Alfa-2a for Further Processing

---------- ------ was shipped to Nutley ----------. The ---------- were stored at ----------pending testing, issuance of a certificate of analysis and release by Nutley QC. Final release at Nutley was based on the acceptance of testing performed at ---------- and a positive identity test ----------performed by Nutley QC. The release IFN must meet all release specifications for IFN.

D. CONTAINER/CLOSURE SYSTEM (Vol 4.15, p.165-166)

Purified IFN alfa-2a was stored in ---------- bottles with ---------- closure. The container/closure system was ----------

H. PURIFIED INTERFERON STABILITY (Vol. 4.15, p. 168-202)

1. Storage of Biomass and Process Pool Intermediates

-------- biomass from -------- IFN was shown to be stable for ----------.
[

]

[

]

Reviewer's comments: ----- different ---------- processing samples were investigated for stability. Based on an evaluation of the data, samples from ---------- processing steps could be held for --- days at ----------^{o}C. Storage periods for ---------- stored at --------^{o}C will be revised as more stability data become available.

2. Final Product Stability

Accelerated stability studies were performed with batch ---------- ---------- ----------. The results of accelerated stability studies indicate the following:

- ---------- were within specification up to -- months at ---^{o}C. At ---^{o}C, ---------- increased after -- months of storage.
- All samples were within specifications for ---------- when stored at -------. Although samples stored at ---^{o}C were within specified limits for ---------- an increase in degradation products (---------- was observed.
- All samples were within ---------- specifications when stored at --^{o}C. At ---^{o}C and ---------- were observed.
- The ---------- did not significantly change over time even at ---^{o}C.

[

]

[

]

Reviewer's comments: --------- month stability data were submitted in the BLA for the ----------. The sponsor claimed a dating period for ---------- IFN of --- months, based on comparable degradation profiles under accelerated storage conditions between ---------- and ------- IFN. Due to the limited stability data, the reviewer does not feel that an accurate assessment of dating period could be achieved at this time.

I. STORAGE AND SHIPMENT OF PURIFIED INTERFERON (Vol. 4.15, p.203)

Purified IFN alfa-2a in solution is stored ----------
[

]

LOT AND BATCH NUMBERING SYSTEM FOR INTERFERON ALFA 2a

[

]

DEFINITION OF A BATCH

The initiation of a production lot is defined as [

]

SUMMARY OF BATCHES

1. Overview of Comparability and Co-mixture batches : attachment #13
2. Interferon alfa-2a and PEG reagent manufacturers by bulk lots: attachment #24
3. Interferon production consistency batches: attachments # 39-41
4. Complete list of batches of purified IFN produced in ----------: this review page 74
5. Information relevant to other batches is given in the corresponding section of this review

BLA TIMELINES

CMC Pre-BLA meeting	March 23, 2000
Receipt of BLA	May 22, 2000
Committee Formation	May 26, 2000
First Committee Meeting	June 12, 2000
Filing Meeting	July 5, 2000
Filing Action	August 7, 2000

Pre Mid-Cycle Meeting October 19, 2000

Mid-Cycle Meeting October 26, 2000

End-of-Review April 12, 2001

Pre-Approval Inspection EU [

]

Action Letter Planned for ----------. Final date pending on complete review by Review Team.

MAJOR DEVELOPMENTS THAT OCCURRED DURING THE REVIEW PERIOD

1. HLR informed CBER (Bill Schwieterman) on October 13, 2000 that ----------will be withdrawn from the BLA, due to failure to demonstrate PK comparability between the phase III material (---------- ----------The problem was that no comparability PK study was performed between the clinical vialed material and the commercial vialed material. The sponsor then proposed a new study for vial-to-vial comparison that would not be completed until April 2001. This will be around the timing of the end-of-review period. Considering that the 10-month review cycle for this BLA ends in mid-March 2001, the data from PK comparability would be needed early in February at the latest, to allow sufficient review time.

The pre-approval inspection of the ---------- manufactured) was officially cancelled (e-mail from Jay Siegal and Sharon Risso, dated 1-22-2001). No new date has been set for the ---------- pre-approval inspection.

2. In an amendment dated October 20, 2000, the sponsor informed CBER of the following problems:

[

]

- In addition to the new contaminants found in the drug product, production was affected by other facility-related issues at Nutley. The pre-approval inspection of the Nutley facility was put on hold. A new date for pre-approval inspection of Nutley has not been decided at this time (Jay Siegal's email of 1-22-2001).

- It was not clear if the registration lots (containing the contaminants) were used in any comparability PK studies. If this was the case, the presence of contaminants may invalidate the PK data.

3. As CBER was getting ready for the ---------- inspection, the sponsor informed John Finkbonher that the ---------- facility would not be ready for inspection planned for ---------- due to problems associated with out-of-specification values for ----------. The Pre-approval inspection of the ---------- facility was cancelled. A new date for pre-approval inspection has not been set at this time (Jay Siegal's email of 1-22-2001).

4. In December 2000, HLR informed CBER (Emmanuel Petricoin) that the sponsor planned to withdraw the ---------- from the BLA, leaving ---------- as the commercial product intended for registration. This was due to failure to demonstrate PK comparability between the phase III material and the ----------

5. On January 2, 11 and 12, 2001, the sponsor contacted CBER (Nga Nguyen) to request advise on issues that are related to the planned decision to withdraw ----------. Summaries of the incoming telecons were sent to Jim Crim for distribution to the Review Committee. With the withdrawal of ----------, the sponsor needed to submit [

]

6. In January 2, 2001, the sponsor submitted the required ---------- ---------- ---------- It appears that the new batches were produced with interferon alfa-2a manufactured before the problem with ---------- was found. It was not clear if the batches of drug product ---------- also contained the ---------- ----------l contaminant that was observed in PEGASYS, ---------- **registration lots** ----------.

7. An internal meeting was conducted on 1-18-2001 to discuss decisions about pre-approval inspections and request for additional information that should be

communicated to the sponsor at this time. That includes (i) a complete description of the lineage of batches and any problem associated with the batches (interferon alfa-2a, pegylating reagent) that were used in producing peginterferon drug substance, (ii) a complete description of the lineage of batches and any problem associated with the batches (peginterferon drug substance) that were used in producing peginterferon drug product and, (iii) purpose of batch (development, consistency, validation, stability, support, registration, PK studies, etc..). The following CBER staff were present at the telecon: Amy Rosenberg, Earl Dye, Chip Petricoin, Barry Cherney, David Green, Glen Jones, Carol Renhopf, Julia Lukas, Jim Crim, Karen Winestock and Nga Nguyen.

8. On 1-19-2001, Chip Petricoin communicated this request to Debra Savuto in the presence of Barry Cherney, Jim Crim, Karen Winestock and Nga Nguyen. Debra Savuto indicated that she would prepare the data and fax them to Jim Crim for distribution and preliminary review before submitting the supplement to the BLA file.

9. On 1-22-2001, a decision was made (Jay Siegal and Sharon Risso) to send the CR letter as soon as possible, outlining all current deficiencies. It was also decided that the inspections should not be scheduled until appropriate consistency lots made after resolution of manufacturing-related problems are available for review and approval.

UPDATED STABILITY DATA RECEIVED DURING REVIEW PERIOD

In a communication dated August 31, 2001, HLR provided the following information.

- Stability update for registration and supporting batches filed in support of the BLA

- Certificates of analysis for the final drug product registration batches filled into vials. The material was [

]

- Certificates of analysis for ---------- are provided to replace the copies, which were submitted with the BLA, due to discrepancies. The discrepancies arose during the final stage of product testing when method improvements were in the process of being implemented at the time of testing registration and stability batches. The methods impacted by the changes were ----------, new methods and specifications described in the BLA were introduced. For the ----------, specific activity reporting ---------- was added.

A summary of updated data regarding IFN and peginterferon drug substance is given below.

1. Updated Stability Data for IFN

Sample	Use	Stability provided	BLA stability	Storage

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Reviewer's comments: No difference in stability between IFN alfa-2a batches produced with ---------- or ----------FN was seen in the accelerated stability study. Real time stability studies are on- going for a total of ----- months.

With this update, there are -- months stability data for ---supportive batches of ---------- ---------- IFN and -------- registration batch of ---------- ---------- ----------IFN. There are -- months stability data on ----- registration batches ---------- IFN. Approval of dating period for ---------- ---------- interferon will be based on real time stability data for registration batches, -- months at the most at this time.

2. Updated Stability Data for Peginterferon Drug Substance

Data from ------- registration lots produced at the --------manufacture scale with
[

]

---- months stability data from ------ supportive lots (----------) registration lots, produced at the -------- manufacture scale with ---------- interferon are submitted with this update.

Updated stability data at the recommended storage temperature of –70^{o}C are summarized below.

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**Reviewer's comments: With this update, there are -- months stability data for --registration batches of pegylated interferon drug substance (----------)
and ----- month stability data for the ---- registration batch (----------reagent). There are -- months stability data on ------- supportive batches of peginterferon drug substance. Stability studies are ongoing for the remainder of the --- month stability program.
Storage under accelerated conditions (----------) resulted in unacceptable protein degradation in all lots.**

Approval of dating period of peginterferon drug substance will be based on real time stability data for registration batches, -- months at the most at this time.

ADDITIONAL BATCH OF PEGINTERFERON DRUG SUBSTANCE: CMC REVIEW

Following withdrawal of peginterferon produced from ----------, HLR amended the BLA to provide the following information on January 12, 2001:

[

]

Reviewer's comments: New parameter values for the ---------- were not described in this communication. The sponsor did not indicate when the ---------- facility would be expected to be ready for pre-approval inspection.

[

]

Reviewer's comments: Chip Petricoin indicated that the revised ---------- procedure was not absolutely identical to the BLA procedure. Thus, this change represents a change in process. In the BLA, the sponsor indicated that the first ------- batches after a change would be fully characterized and should be within all release specifications (as per BLA Version 2.1, not per proposed "Specifications version 3.0"). It is not clear how many consistency batches of interferon alfa-2a have been produced after the problem with inefficient removal of ----------.

1. In-Process Testing Results

- **Pegylation reaction**

[

]

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- **Process Step Yields**

--g batches: ----------

2. Release testing Results

Attachment # 57 shows BLA release specifications, analytical results and certificates of analysis for registration batches ----------.

The same ---------- ---------- were obtained upon analysis of the -- registration batches by ----------

3. Extended Characterization Results

Extended characterization was performed by [

]

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Results of in-process and release testing, extended characterization and stability studies indicated consistency between the --------- drug substance batches.

Reviewer's Comments: The interferon lot number for peginterferon drug substance lot ---------- have been identified (Vol. 4.8-10) as ---------- ----------. The sponsor did not identify the interferon lot number for the additional ---------- drug substance lot ----------.

CONCLUSIONS AND RECOMMENDATIONS

I have reviewed the Chemistry, Manufacturing and Control (CMC) of peginterferon alfa-2a drug substance and have the following comments and recommendations. These comments are also given in bold characters in the body of this review.

In general, the sponsor clearly and adequately described the processes involved in the production, purification and structural characterization of the components of pegylated interferon 2a drug substance. Analytical methods that were used for production and characterization, and their validation and impurity profiles were

also depicted in details. Reprocessing of specific steps was clearly illustrated with regards to compliance with strict requirements before and after reprocessing.

Values from the certificates of analysis of ---------- batches were comparable and were within established specifications. The results supported analytical comparability of PEG reagent made at the --------- and -------- facilities using ------- manufacturing process. Data was also provided to support comparability of commercial -------- process to clinical ------ process for pegylating reagent manufacture.

Interferon alfa-2a batches manufactured in ---------- ----------fulfilled all BLA release specifications and were comparable to --------- interferon.

Pegylated interferon alfa-2a registration batches, made with commercial material, were in compliance with BLA specifications with regards to physico-chemical characteristics and biological activity. Physico-chemical comparability of the phase III material ---------- pegylating reagent) manufactured at the --- g scale with the commercial material (---------- pegylating reagents) manufactured at the --- g was demonstrated by release testing results and extended characterization including co-mixture experiments.

The sponsor provided adequate lineage for ---------- consecutive batches of peginterferon alfa-2a drug substance. The batches were included in process validation for the purpose of establishing physico-chemical comparability of product components. They represented both registration and supportive batches produced with ---------- as well as ------- IFN and with ---------- as well as ---------- pegylating reagent (Tables 1 and 2 of this review; also attachment #24).

Note: At the January 18, 2001 internal telecon**,** there was a question about the fate of the bulk lots that were produced between lots ----------. It appeared that the commercial lots submitted in the BLA were not continuous lots. This question has been answered in attachment #24: bulk lots ----------were manufactured with --------- (not ----------) interferon alfa-2a, and thus were not commercial registration lots.

The sponsor also provided a listing of comparability and co-mixture lots (attachment #13) and of batches used as consistency batches for the various steps in interferon production (attachments #39-41).

In summary, physico-chemical comparability was demonstrated for:

[

]

I have a few comments and requests for clarification and/or additional information. Comments and questions are related to peginterferon drug substance only. Chip Petricoin will address issues related to the drug product.

1. ------ batches ----------batches of ---------- batches of ---------- batches of ---------- pegylating reagent were used to manufacture peginterferon at various stages of development and production. Appropriate lineage of peginterferon drug substance components was given in attachment #24 for registration and supportive batches. This information was not provided for all peginterferon drug substance manufactured with ----------interferon alfa-2a. This should not be an issue since no production problem was found with interferon produced in ---------- and since the registration batches were manufactured with ---------- (not -------) interferon.

2. Until March 1999, peginterferon Reference Standard lot ----------, with assigned units of ------- U/mL (corresponding to -------/ng) was used. This batch was calibrated against the WHO interferon Reference Standard. During the course of product development, a new peginterferon Reference Standard, ----------was introduced in March 1999. This standard was NOT calibrated against the WHO interferon Reference Standard, but was ---------- U/ng). The amendment requesting change in reporting of unitage (----------) was reviewed and approved in August 1999.

3. The sponsor indicated that a new peginterferon Reference Standard will be prepared from commercial ----- g material using ---------- ----------interferon. The new Reference Standard will be qualified by calibration against WHO IFN Reference Standard, as opposed to the current ------ method that was used to qualify ----------. The rationale for switching back to the former unitage system (by qualification against WHO IFN standard, as opposed the approved new method based on -------) was not clearly enunciated in this BLA. In an outgoing telecon requesting clarification on this issue, (December 5, 2000), Debra Savuto indicated that returning to calibration against the WHO standard was necessary to prepare the company for global harmonization. Both systems of reporting biological units are acceptable, except for the unit value that is 7 x higher if qualified against the

WHO IFN standard. It is recommended that the sponsor firmly chooses, and consistently uses one of the two reporting systems. This issue is addressed in the "Questions to the Manufacturer" section.

4. The source (----------) and batch number of the pegylating reagent intended for the new peginterferon Reference Standard were not clearly identified. Neither was the batch number of ---------- ---------- interferon intended for this new peginterferon Reference Standard. This issue is addressed in the "Questions to the Manufacturer" section.

5. Multiple facilities were involved in manufacturing, packaging, warehousing and distribution of pegylated interferon alfa-2a, ---------- and vial [
[

]
manufactured, packaged and distributed by Nutley. Thus, it is important to ensure that hold times and shipping conditions were clearly validated and established for each component of the peginterferon alfa-2a system to preserve product quality, integrity and potency.

The sponsor provided validated data on acceptable hold times during ----------
---
---
interferon alfa-2a ---------). No information was provided on shipping conditions and hold times for the pegylating reagent and for the pegylated drug substance. This issue is addressed in the "Questions to the Manufacturer" section.

6. In the original ----------, storage conditions for the pegylating reagent [

] were provided for review. The discrepancy in storage and stability testing temperature was not clearly addressed in the BLA. This issue is addressed in the "Questions to the Manufacturer" section.

7. Due to the numerous changes that were introduced after phase III, human and animal PK comparability between the phase III material (----------
---------- and the commercial material (---------- ----------) must be demonstrated. At this time, the sponsor did not demonstrate PK comparability between phase III material and ----------

Nor was comparability established between Phase III material and commercial vialed material using ----------. As a consequence, the sponsor withdrew ---------- peginterferon alfa-2a drug substance and drug product from consideration in November 2000 and January 2001, respectively. To fulfill the regulatory requirement for submitting three consecutive registration batches to the BLA, the sponsor submitted data on ---------additional drug substance batch ---------- and -----additional drug product batches ---------- (using --------- as the pegylating reagent) on January 12, 2001. The amendment was distributed for review on January 16, 2001. The sponsor provided the batch number for ----------, but not for ---------- ---------- interferon that was pegylated to generate drug substance batch ----------. This issue is addressed in the "Questions to the Manufacturer" section.

8. The sponsor established programs for appropriate certification of incoming materials and their segregation from those released by quality management. ----------, respectively) and ---------- respectively) were established and strictly enforced.

9. Interferon alfa-2a contains a small amount of ---------- material for which a specification of ------- was established. This ---------- component was also [

] This issue is addressed in the "Questions to the Manufacturer" section.

10. [

]

11. The proposed specifications and analytical methods, which were developed in parallel with clinical and technical development programs, reported oligoPEG IFN and diPEG IFN separately (as in Pre-BLA package). In the BLA, specifications were revised to report the sum of diPEG IFN and [

]not change the -- % BLA specifications. This revision did not significantly affect evaluation of the drug substance identity, purity and quality.

12. Stability data provided with this BLA indicated that the phase III material demonstrated adequate stability for --- months. The sponsor stated that this stability profile was an appropriate predictor of shelf life based on the demonstration of analytical comparability between the phase III and commercial materials and claimed the 18-month shelf-life for commercial materials. This request would be acceptable only if the materials exhibited comparability with regards to analytical and pharmacological characteristics. It would be acceptable only if the sponsor concurred to provide updated stability data to support the proposed dating period. As it turned out, ---------- ---------- were withdrawn from consideration for lack of PK comparability to the Phase III product. Of the 2 remaining registration drug substance batches made with ----------pegylating reagent, -------- month (updated) stability data are available for --------- batch. ------ month updated stability data are available for the ---------- batch. Even with updated stability data (please see page 81 of this review), the information remains too limited to allow for an accurate assessment of long-term stability. This issue is addressed in the "Questions to the Manufacturer" section.

13. The removal factor for process-related impurities indicated that the ----------
[

] A review of data submitted by the sponsor in January 2001 provided assurance that the ---------- interferon batches submitted with this BLA were manufactured before problems with out-of-specification for ---------- were described on November 3, 2000.

[

]

[

] These issues are addressed in the “Questions to the Manufacturer” section.

14. There was no discussion on the number of sampling points prior to final delivery of purified water II to the equipment or prior to its use in preparing ---------- This issue is addressed in the “Questions to the Manufacturer” section.

15. The sponsor did not clearly describe procedures for ensuring that the correct chemicals [

]
These issues are addressed in the “Questions to the Manufacturer” section.

16. The sponsor did provide sufficient information on the number of master and working cell banks, and on their storage at ----------). However, the following information was not provided in the BLA: Were *E. coli* master and working cell banks for interferon alfa-2a segregated from mammalian cell banks? Was accessibility restricted to authorized personnel only? Were the liquid nitrogen storage tanks locked? Were the storage tanks equipped with temperature alarms and monitors? These issues are addressed in the “Questions to the Manufacturer” section.

17. The sponsor indicated that retest intervals for working cell banks was -- years but did not discuss procedures to follow if IFN alfa-2a production was interrupted for periods exceeding the -- years retest interval. This issue is addressed in the “Questions to the Manufacturer” section.

18. In version 3.0 of “Specifications”, the sponsor proposed to remove ----------[

] This issue is addressed in the “Questions to the Manufacturer” section.

19. The following tests were part of ------- release specifications but were not performed at ---------- for product release: ---------- [

[

]

This issue is addressed in the “Questions to the Manufacturer” section.

20. [

]

These issues and other questions that arose during the review of this BLA are addressed in the “Questions and Comments to the Manufacturer” section. I have reviewed all batches (including those made with ----------) but only formulated questions pertaining to peginterferon produced with ---------- pegylating reagent, in view of the decision by HLR to withdraw ---------- peginterferon batches from consideration.

OVERVIEW OF BLA 103964

BLA #	**103964** (**ORIGINAL SUBMISSION**)
Product	PEGASYS™ (PEG-IFN; Peginterferon alfa-2a; peginterferon)
Manufacturer	Hoffmann-La Roche, Inc., Nutley, NJ
Sponsor	Hoffmann-La Roche, Inc., Nutley, NJ
Proposed Use	Treatment of Patient with Chronic Hepatitis C; 180 mg SC once a week for 48 weeks
Special Request	Priority Review
User Fee ID Number	----------
Electronic Submission	None (in the electronic format proposed before June 1, 2000)
Reviewer	Emanuel F. Petricoin (DTP/OTRR/CBER/FDA)
Review Responsibility	CMC (Drug Product)

DRUG PRODUCT

I. Dosage forms:

⇒ 180 ?g/mL, 1 mL fill in a 2 mL vial

⇒ ----------

REGISTRATION BATCHES SUBMISTTED TO THE BLA:

1. [

]

Product Characteristics

1. Appearance: clear colorless liquid free from particulate matter
2. Containers: flint vials
3. ----------
4. ----------
5. pH: 6.0 ± 0.1
6. ----------
7. ----------

II. Primary Packing Components

1. Vials: 2 mL ---------- glass vials, 13 mm finish
2. Stoppers: 13 mm ---------- stopper
3. Seals: 10 mm, aluminum lacquered, flip-off cap

A. Vials:

---------- glass ---------- vials were selected to facilitate inspection of the product for particulate matter and/or turbidity. PEGASYS is unstable when exposed in a light chamber at ----------. The product is therefore stored protected from light in its secondary packaging at 2^{o} to 8^{o} during distribution and storage in pharmacies.

The glass containers are fabricated ----------

Each shipment of finished containers is tested during incoming material inspection to make sure the glass containers meet (----------

---

Suppliers of the 2 mL glass container:

[

]

Submitted to the BLA are the drug master file letter of authorization, component description and directions for testing - these appear adequate.

.

B. Stoppers:

[

]

Submitted to the BLA are the drug master file letter of authorization, component description and directions for testing (----------closure must be ----------
---

C. ----------flip-off seal

The ---------- seals are non-contact material and only serve to apply and maintain mechanical pressure on the --------- closures (180 ?g/mL vial will have a red flip-off seal). The supplier of the seal:

[

]

D. Secondary Packaging

All vials will be labeled with a pressure sensitive label that is pre-printed and supplied on a roll. The label is coded with a lot code and expiration date during the labeling operation. One labeled vial is placed in a preprinted carton and one patient and physician insert placed in concomitantly. The carton is closed and then placed into a larger shipper box, sealed, then labeled and palletized for shipment.

III. Stopper Extractables

PEGASYS vials evaluated in this study were stored at ---------- months and at ---------- C for an additional -- months. The vials were stored in ----------
[

]

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INGREDIENT	*SPECIFICATION*	**QUANTITY PER ML**
Peginterferon alfa 2a		180 ? g
Sodium acetate trihydrate		2.617mg
Acetic Acid glacial		0.0462 mg
Sodium Chloride		8.0 mg
Benzyl alcohol		10.0 mg
Polysorbate 80		0.05 mg
Water for Injection		q.s. 1.0 mL

Final pH 6.0 ± 0.1 If necessary pH may be adjusted with acetic Acid (10% w/v) and Sodium Acetate Trihydrate (10%w/v)

A. BATCH FORMULA

[

]

Release Testing:

1. ---------- ----------
2. pH 6.0 ± 0.5

3. Density ----------
4. Identity (----------) ----------
5. Identity (----------) ----------
6. Identity (----------) ----------
7. Purity (---------- ----------
8. Purity ---------- ----------
9. Purity(---------- ----------
10. Purity (---------- ----------
11. Consistency of Pegylation: (----------)

[

]

1. Peginterferon alfa 2a ----------

[

]

12. Purity (----------)

[\

]

15. Specific Biological Activity ----------

[

]

b. [ ]

c. pH 6.0±0.5

d. [ ]

e. Identity test [ ]

identity test [ ]

f. purity ----------

Purity ----------

g. Benzyl alcohol ----------

h. ----------

⇒ Purity ----------

j. Specific biological activity ----------

k. Sterility: bulk ----------

l. Sterility---------- ----------

[

]

IX. IMMUNOGENICITY STUDIES

Neutralizing antibodies were seen at 8 weeks post-treatment in 1-4% of the patients treated with PEGASYS as opposed to 11-17% with interferon alone, suggesting that pegylation decreased the immunogenicity of the IFN molecule. A small number of antibody positive patients (14%) with low antibody titers 8 weeks after the end of a 48 week treatment period were sustained virological responders, suggesting that the presence of detectable levels of antibody does not necessarily preclude a therapeutic effect.

X. DRUG PRODUCT STABILITY

Submitted to the BLA in support of the stability program is:

1. material manufactured using the ------- material (-- lots manufactured at the ----------
2. ---- lots peginterferon (----------) produced at the ----------
3. No lots at the ---------- process

Data submitted demonstrate that -- lots of the ---------- material are stable for up to --- months (data for the other -- lots for up to --- months) Stability data is provided showing stability of the ---------- at the -- month time point. The stability program initiated for the vials include testing every -- months until the ----------, then every -- months up to --- months.

Stability indicating tests:

[

]

XI. Shipping Qualification Summary:

⇒ In facility controls: The final dosage form of PEGASYS will be stored in controlled refrigeration units when not being staged for labeling and secondary packaging.

⇒ Transport from Nutley, New Jersey to the Distribution Center: The final dosage form of PEGASYS will be transported from Nutley via ----------. The -------- is equipped with temperature recording devices and failure warning systems.

⇒ Transport from the Distribution Center to domestic locations: A qualified insulated container system consisting of and ----------

All domestic shipments will be made using an overnight delivery company to minimize exposure to adverse conditions.

XII Review of other Amendments

Amendment submitted on September 15, 2000

Drug product specifications and methods for vials are re-issued to reflect ---------- ---------- method revisions, consistent with drug substance specifications and methods. The change is that ----------

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BLA 103964/0
Pegylated Interferon Alfa-2a
CMC, Drug Substance and Drug Product

QUESTIONS AND COMMENTS TO THE MANUFACTURER

CMC DRUG PRODUCT QUESTIONS AND COMMENTS TO THE MANUFACTURER

1. **Please provide batch numbers of the pegylating reagent and interferon alfa-2a lots that were used to manufacture the new peginterferon reference standard described in Vol. 4.8, pages 126-130.**

2. **Please discuss how the new peginterferon reference standard would be qualified. Would calibration against the WHO interferon standard serve as the basis for qualification, as opposed to the currently approved method based on -------? It is highly recommended to select and consistently use one of the two qualification methods in assessing and reporting peginterferon alfa-2a biological activity.**

3. **When formulating peginterferon by mass, was the mass of the SWP2 40 ---------- considered?**

4. **How was the ---------- pegylating reagent determined? Was it at the center of a distribution of MW?**

5. **Please describe hold conditions (temperature, time) for -------- pegylating reagent, and for the pegylated drug substance prepared with --------- pegylating reagent.**

6. **Please clarify shipping conditions for -------- pegylating reagent from the Alabama facility to the Nutley facility.**

7. **Storage conditions of the pegylating reagent as specified by ---------- Please clarify the real-time long-term storage conditions for the pegylating reagent.**

8. **Please provide stability data for ------ pegylating reagent.**

9. **Interferon alfa-2a and pegylated interferon alfa-2a contain approximately ----------. Was the immunogenicity potential of this ---------- product determined?**

10. **Please be informed that dating period for both ---------- interferon and the corresponding pegylated drug substance will not be based on the stability of supportive ------- materials, but will be based on real-time stability data generated for the registration batches. This is also true for the PEGASYS drug product, which at this time only has real time stability data submitted for the ---------- time point.**

11. **Please comment on the rationale for removing ---------- [**

]

12. **Please describe conditions for ---------- of interferon. For example, ----------**
[

]

13. **Please comment on the number of sampling points for purified water II (PWII) prior to its final delivery to the equipment or prior to its use in ----------**

14. **Please describe procedures to ensure accuracy and precision in**
[

]

[

]

15. **Please comment on procedures to ensure integrity of master and working cell banks for interferon alfa-2a. Specifically, were *E. coli* master and working cell banks for interferon alfa-2a segregated from mammalian cell banks? Was accessibility restricted to authorized personnel only? Were the storage ---------- locked? Were the storage ------- adequately equipped with temperature alarms and monitors? How often was the ---------- temperature checked?**

16. **Interferon alfa-2a working cell banks are currently retested every -- years. How would retest schedule be affected if IFN alfa-2a production was interrupted for a period exceeding -- years?**

17. **In the revised specifications version 3.0 for interferon alfa-2a, ----------.**
[

]

18. **Please provide batch number for the ---------- ---------- batch that was pegylated with -------- to produce the additional (third ----------) peginterferon drug substance ---------- submitted to the BLA in January 2001.**

19. **A question which did not arise from the review of the BLA but from a communication by the sponsor reporting out-of-specification for ---------- ---------- in routine production batches made after November 3, 2000:**
[

]

20. **Please provide manufacturing information on lots ---------- and ---------- manufactured by clinical porsonnel.**

21. **Drug product registration lots have not been manufactured consecutively. Furthermore, ---------- was made with a non-consecuttivc ---------- drug product batch (----------).**

22. **Please provide data to validate that the three drug product registration batches were produced with the ----------**

23. **Please provide data to validate that the ---------- drug product registration batches do not contain any contaminating ----------**

24. **Investigations into the ---------- contamination of drug product were [**

]

25. **Please provide data that the drug product lots used for all ongoing trials involving the use of animal and/or human subjects are prepared using [**

]

26. **Please provide details the corrective action plan for the removal of the ----------**

27. **As a result into the ---------- investigation, please provide information ----------**

28. **Please provide information concerning the distribution and ----------**

29. **Please provide data concerning the observed --% decrease in ----------**

30. **Were drug product lots produced using the incorrect ----------.**